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Falsely Elevated Levels of Pancreastatin, a Neuroendocrine Tumor Marker

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Abstract

Chromogranin A and pancreastatin are neuroendocrine tumor markers. A 69-year-old female presented for diagnosis and management of a potential neuroendocrine tumor related to nausea, vomiting, and diarrhea for over 40 years. Initial neuroendocrine tumor work-up only revealed a slightly elevated chromogranin A level. Computed Tomography (CT) of chest, abdomen, and pelvis did not find neuroendocrine tumors. Her pancreastatin levels were higher than upper limit of normal at one commercial laboratory with a pancreastatin assay developed in-house but entirely normal in another which used a validated assay. The patient in this case illustrates an often-neglected cause of false positive test result, namely, spurious assay. Clinicians need to critically analyze a given test result in the context of clinical history, physical examination findings, other biochemical test and imaging results, and histological evidence, and to determine if an unexpected test result is false positive.

Case Report

A 69-year-old female presented for diagnosis and management of a potential neuroendocrine tumor. She had started to take niacin for severe headache in her youth and developed flushing after taking niacin. She had had nausea, vomiting, and diarrhea since age 23. She had seen numerous doctors without clear diagnosis. The symptoms worsened in the last 4 years. She could tolerate only a few food items; all other foods made her nauseous. She had up to 10 bowel movements with loose stool on any given day. Her weight decreased from 153 to 125 lbs. She had lower abdominal pain without tenderness for years but had no asthma-like symptoms. The patient strongly suspected that her symptoms were due to an underlying undiagnosed neuroendocrine tumor. Her past medical history included adrenal insufficiency for which she took hydrocortisone and fludrocortisone. She had no family history of endocrine tumors. She took many supplements. Her vital signs were stable. She appeared thin with a Body Mass Index (BMI) of 20.6 kg/m^2. Other physical examination findings were unremarkable. Available laboratory test results from another hospital 2 months before showed that chromogranin A level was 137 ng/ml (normal < 93, normal renal function, not on anti-acid treatment), and urine 5-hydroxyindoleacetic acid (5-HIAA) 7.7 mg/24 h (normal < 8). Computed Tomography (CT) of chest, abdomen, and pelvis performed 1 month and 13 years before each demonstrated liver cavernous hemangiomas but otherwise unremarkable findings.

The overall suspicion of neuroendocrine tumor (including carcinoid) was deemed low. As the patient was anxious of the slightly elevated chromogranin A level which could be caused by undiagnosed atrophic gastritis, fasting levels of chromogranin A, pancreastatin, and gastrin were ordered. Chromogranin A level remained slightly elevated at 106 ng/ml (normal < 93) but gastrin was normal (19 pg/ml with normal < 100). Surprisingly, pancreastatin level was >1920 pg/ml (normal < 88), measured by a commercial laboratory (Lab A) that was contracted with her local clinical laboratory (Table 1). The extremely elevated pancreastatin level caused more anxiety in the patient and reaffirmed her idea that she had an undiagnosed neuroendocrine tumor. Blood specimen was then sent to another commercial laboratory (Lab B) which used a pancreastatin radioimmunoassay (RIA) that had been validated in a published series on pancreastatin performance in neuroendocrine tumor diagnosis and follow-up. The pancreastatin result measured by Lab B was 40pg/ml (normal 10-135). To further confirm that the Lab A pancreastatin assay was not accurate, a month later, blood specimens drawn at the same time were simultaneously sent to Lab A and Lab B. Pancreastatin level measured by Lab A was still > 1920 pg/ml (normal < 88) but that measured by Lab B was 67 pg/ml (normal 10-135), respectively. It was concluded that the pancreastatin assay of Lab A was spurious. The patient was reassured that she did not have neuroendocrine tumor. The cause of her symptoms remained undiagnosed.

Discussion

Neuroendocrine tumor markers play important roles in the diagnosis and follow-up of patients with suspected neuroendocrine tumors [1]. General neuroendocrine tumor markers include chromogranin A, neuron-specific enolase, and lately pancreastatin, and they are usually elevated in patients with a substantial burden of any neuroendocrine tumors. Due to various reasons, false elevation of the levels of neuroendocrine tumor

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	Assay	Reference range	Result 1	Result 2
Lab A	Radioimmunoassay developed in-house	0-88 pg/ml	> 1920	> 1920
Lab B	Radioimmunoassay validated in a published series [3]	10-135 pg/ml	40	67

Table 1: Pancreastatin levels measured by two commercial laboratories

markers is fairly common in clinical practice. Chromogranin A, for example, is elevated in patients on proton pump inhibitors or H_2 blockers, with atrophic gastritis, or with renal insufficiency [2]. Pancreastatin has been considered as potentially the best marker of neuroendocrine tumors [3,4]. Pancreastatin is a degradation product of chromogranin A; it consists of 52 amino acid residues and corresponds to amino acid residues 250-301 of chromogranin A. One advantage of pancreastatin over chromogranin A is that the former is not affected by anti-acid treatments [5]. Pancreastatin is measured by immunoassays. The best validated assay is a radioimmunoassay using an antiserum raised against aporcine pancreastatin fragment which cross reacts with human pancreastatin; this assay is used by Lab B. RIA is an immunoassay based on the principle that radiolabeled specific antibody to a molecule competes with unlabeled antibody in binding with the molecule [3].

The pancreastatin results from Lab A certainly are false positive based on the following lines of evidence. First, the patient's likelihood of having an undiagnosed neuroendocrine tumor is very low. Her over 40 years of history of diarrhea, slightly elevated chromogranin A, and absence of tumors in the pancreas, intestine, or lungs are not compatible with a neuroendocrine tumor diagnosis, as diarrhea-causing neuroendocrine tumors are almost always bulky with remote metastasis [6]. Second, pancreastatin and chromogranin A levels usually parallel each other thus the extremely elevated pancreastatin levels measured by Lab A and only slightly elevated chromogranin A levels are very unusual [3,4]. Third, the pancreastatin levels measured by Lab B which uses a validated RIA are entirely normal. Publically available information from Lab A suggests that Lab A developed a pancreastatin RIA of their own, not with the antiserum used by Lab B. The cause of the slightly elevated chromogranin A levels in this patient remained unclear.

False positive test results are a serious clinical problem in neuroendocrine tumor diagnosis and follow-up, and can lead to patient anxiety, unnecessary further testing and imaging, and even invasive procedures [7,8]. Neuroendocrine tumor marker test results are interfered by physiological conditions, comorbidities, and medications [1,2]. The patient in this case illustrates another, often-neglected cause of false positive test result, namely, spurious assay. On the other hand, an apparently false positive result may be true positive in a previously unrecognized condition [9]. Clinicians need to critically analyze a given test result in the context of clinical history, physical examination findings, other biochemical test and imaging results, and histological evidence, and determine if an unexpected test result is false positive or may suggest a novel condition.

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